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\* \* \* \* \* STN Columbus \* \* \* \* \*

FILE 'HOME' ENTERED AT 11:42:53 ON 04 AUG 2003

=> file medline, biosis, dgene, wpids, jicst, fsta, embase, uspatful,  
COST IN U.S. DOLLARS  
FULL ESTIMATED COST

	SINCE FILE ENTRY	TOTAL SESSION
	0.84	0.84

FILE 'MEDLINE' ENTERED AT 11:45:22 ON 04 AUG 2003

FILE 'BIOSIS' ENTERED AT 11:45:22 ON 04 AUG 2003  
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FILE 'USPATFULL' ENTERED AT 11:45:22 ON 04 AUG 2003  
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

=> s insulin () agonist  
L1 3052 INSULIN (W) AGONIST

=> s l1 and antagonist  
L2 54 L1 AND ANTAGONIST

=> s l1 and hypoglycemia  
L3 9 L1 AND HYPOGLYCEMIA

=> d l3 ti abs ibib tot

L3 ANSWER 1 OF 9 MEDLINE on STN

TI (A-C-B) human proinsulin, a novel **insulin agonist** and intermediate in the synthesis of biosynthetic human insulin.

AB. The hormone insulin is synthesized in the beta cell of the pancreas as the precursor, proinsulin, where the carboxyl terminus of the B-chain is connected to the amino terminus of the A-chain by a connecting or C-peptide. Proinsulin is a weak **insulin agonist** that possesses a longer in vivo half-life than does insulin. A form of proinsulin clipped at the Arg65-Gly66 bond has been shown to be more potent than the parent molecule with protracted in vivo activity, presumably as a result of freeing the amino terminal residue of the A-chain. To generate a more active proinsulin-like molecule, we have constructed an "inverted" proinsulin molecule where the carboxyl terminus of the A-chain is connected to the amino terminus of the B-chain by the C-peptide, leaving the critical Gly1 residue free. Transformation of Escherichia coli with a plasmid coding for A-C-B human proinsulin led to the stable production of the protein. By a process of cell disruption,

sulfitolysis, anion-exchange chromatography, refolding, and reversed-phase high-performance liquid chromatography, two forms of the inverted proinsulin differing at their amino termini as Gly1 and Met0-Gly1 were identified and purified to homogeneity. Both proteins were shown by a number of analytical techniques to be of the inverted sequence, with insulin-like disulfide bonding. Biological analyses by in vitro techniques revealed A-C-B human proinsulin to be intermediate in potency when compared to human insulin and proinsulin. The time to maximal lowering of blood glucose in the fasted normal rat appeared comparable to that of proinsulin. Additionally, we were able to generate fully active, native insulin from A-C-B human proinsulin by proteolytic transformation. The results of this study lend themselves to the generation of novel insulin-like peptides while providing a simplified route to the biosynthetic production of insulin.

ACCESSION NUMBER: 92112687 MEDLINE  
DOCUMENT NUMBER: 92112687 PubMed ID: 1730606  
TITLE: (A-C-B) human proinsulin, a novel **insulin agonist** and intermediate in the synthesis of biosynthetic human insulin.  
AUTHOR: Heath W F; Belagaje R M; Brooke G S; Chance R E; Hoffmann J A; Long H B; Reams S G; Roundtree C; Shaw W N; Slieker L J;  
CORPORATE SOURCE: Lilly Research Laboratories, Indianapolis, Indiana 46285.  
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1992 Jan 5) 267 (1) 419-25.  
Journal code: 2985121R. ISSN: 0021-9258.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199202  
ENTRY DATE: Entered STN: 19920308  
Last Updated on STN: 20000303  
Entered Medline: 19920218

L3 ANSWER 2 OF 9 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN  
TI Blood sugar controlling agent for diabetics taking insulin prevents side effects such as **hypoglycemia**.

AN 2000-205896 [18] WPIDS

AB WO 200009147 A UPAB: 20000412

NOVELTY - Blood sugar controlling agent for diabetics taking insulin comprises an insulin receptor agonist and neurotrophin.

ACTIVITY - Antidiabetic.

In streptozocin induced diabetic mice BDNF at 20 mg/kg reduced the maximum decrease in blood sugar levels after insulin was administered at 4.5 U/kg but increased the amount of time blood sugar levels remained depressed.

MECHANISM OF ACTION - Hypoglycemic; **Insulin-Agonist**

USE - As a blood sugar level controlling agent for diabetics taking insulin.

ADVANTAGE - Agent potentiates the effect of insulin, prevents fluctuations in blood sugar levels and thus reduces side effects such as hypoglycemic shock.

Dwg.0/3

ACCESSION NUMBER: 2000-205896 [18] WPIDS  
DOC. NO. CPI: C2000-063613  
TITLE: Blood sugar controlling agent for diabetics taking insulin prevents side effects such as **hypoglycemia**.  
DERWENT CLASS: B04  
INVENTOR(S): NAKAGAWA, T; NAKAYAMA, C; NOGUCHI, H; TAIJI, M  
PATENT ASSIGNEE(S): (SUMU) SUMITOMO PHARM CO LTD  
COUNTRY COUNT: 88

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000009147	A1	20000224	(200018)*	JA	24
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
AU 9951956	A	20000306	(200030)		
EP 1106182	A1	20010613	(200134)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
JP 2000564649	X	20011023	(200202)		
CN 1314819	A	20010926	(200206)		
KR 2001072354	A	20010731	(200209)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000009147	A1	WO 1999-JP4322	19990810
AU 9951956	A	AU 1999-51956	19990810
EP 1106182	A1	EP 1999-937009	19990810
		WO 1999-JP4322	19990810
JP 2000564649	X	WO 1999-JP4322	19990810
		JP 2000-564649	19990810
CN 1314819	A	CN 1999-810064	19990810
KR 2001072354	A	KR 2001-701694	20010208

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9951956	A Based on	WO 200009147
EP 1106182	A1 Based on	WO 200009147
JP 2000564649	X Based on	WO 200009147

PRIORITY APPLN. INFO: JP 1998-226442 19980811

L3 ANSWER 3 OF 9 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN  
 TI Composition for treatment of diabetes with reduced side effects comprises  
 an insulin sensitizer in combination with an anorectic.

AN 2000-147239 [13] WPIDS

AB WO 200000195 A UPAB: 20000313

NOVELTY - A pharmaceutical composition comprises an insulin sensitizer in  
 combination with an anorectic.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:

(1) a method for reducing the side effects of an insulin sensitizer  
 and/or an anorectic administered to a diabetic comprising administering an  
 effect amount of them;

(2) a method for preventing or treating diabetes and impaired glucose  
 tolerance in a mammal by administering to the mammal the sensitizer in  
 combination with an anorectic.

ACTIVITY - Antidiabetic; Anorectic.

The effects of concomitant administration of pioglitazone  
 hydrochloride and mazindol in non-insulin-dependent diabetic mellitus  
 (NIDDM) patients were studied. When pioglitazone hydrochloride (45mg/day  
 p.o.) was concomitantly administered to an NIDDM patient under treatment  
 with mazindol (1.0mg/day p.o.) over the period of 8 weeks, fasting blood  
 sugar decreased by 70 mg/dl, HbA1c decreased by 2% and body weight  
 decreased by 1.0 kg.

MECHANISM OF ACTION - **Insulin-Agonist.**

USE - The composition is useful for preventing and treating diabetes, diabetic complications and for treating impaired glucose tolerance. The composition possesses an increased blood sugar lowering action, blood lipid lowering action or blood insulin lowering action as compared with administration of an insulin sensitizer or an anorectic alone.

ADVANTAGE - Use of the present composition in combination with insulin enables reduction of the amount of insulin used when compared with the amount used at the time of administration of insulin alone. Therefore, risk of blood vessel complication and **hypoglycemia** induction is low.

Dwg.0/0

ACCESSION NUMBER: 2000-147239 [13] WPIDS  
 DOC. NO. CPI: C2000-046089  
 TITLE: Composition for treatment of diabetes with reduced side effects comprises an insulin sensitizer in combination with an anorectic.  
 DERWENT CLASS: B03  
 INVENTOR(S): ODAKA, H; YAMANE, M  
 PATENT ASSIGNEE(S): (TAKE) TAKEDA CHEM IND LTD; (ODAK-I) ODAKA H; (YAMA-I) YAMANE M  
 COUNTRY COUNT: 86  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000000195	A1	20000106	(200013)*	EN	43
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL					
OA PT SD SE SL SZ UG ZW					
W: AE AL AM AU AZ BA BB BG BR BY CA CN CU CZ EE GD GE HR HU ID IL IN					
IS JP KG KR KZ LC LK LR LT LV MD MG MK MN MX NO NZ PL RO RU SG SI					
SK SL TJ TM TR TT UA US UZ VN YU ZA					
JP 2000080047	A	20000321	(200025)		14
AU 9942914	A	20000117	(200026)		
BR 9911656	A	20010320	(200123)		
NO 2000006630	A	20010226	(200123)		
EP 1093370	A1	20010425	(200124)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
CN 1305376	A	20010725	(200164)		
KR 2001043455	A	20010525	(200168)		
US 6329403	B1	20011211	(200204)		
ZA 2000006262	A	20020130	(200217)		54
MX 2000010582	A1	20010501	(200227)		
US 2002086885	A1	20020704	(200247)		
AU 754740	B	20021121	(200305)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000000195	A1	WO 1999-JP3496	19990629
JP 2000080047	A	JP 1999-183299	19990629
AU 9942914	A	AU 1999-42914	19990629
BR 9911656	A	BR 1999-11656	19990629
		WO 1999-JP3496	19990629
NO 2000006630	A	WO 1999-JP3496	19990629
		NO 2000-6630	20001222
EP 1093370	A1	EP 1999-957622	19990629
		WO 1999-JP3496	19990629
CN 1305376	A	CN 1999-807133	19990629
KR 2001043455	A	KR 2000-712502	20001108
US 6329403	B1	WO 1999-JP3496	19990629
		US 1999-380059	19990825
ZA 2000006262	A	ZA 2000-6262	20001102

MX 2000010582 A1  
US 2002086885 A1 Div ex  
Div ex  
AU 754740 B

MX 2000-10582 20001027  
WO 1999-JP3496 19990629  
US 1999-380059 19990825  
US 2001-36208 20011229  
AU 1999-42914 19990629

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9942914	A	Based on	WO 200000195
BR 9911656	A	Based on	WO 200000195
EP 1093370	A1	Based on	WO 200000195
US 6329403	B1	Based on	WO 200000195
AU 754740	B	Previous Publ. Based on	AU 9942914 WO 200000195

PRIORITY APPLN. INFO: JP 1998-183700 19980630

L3 ANSWER 4 OF 9 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN  
TI Composition for treating conditions caused by insulin agonists - e.g.  
**hypoglycemia** and glycogen diseases.  
AN 1998-133629 [13] WPIDS  
AB JP 10007586 A UPAB: 19980330  
The composition which is for treating diseases caused by insulin like  
action comprises hepar parenchymatous cell proliferation factor.  
USE - The agent is used for prevention and/or therapy of diseases  
caused by insulin like action, e.g. **hypoglycemia** and glycogen  
diseases.  
Dwg.0/3

ACCESSION NUMBER: 1998-133629 [13] WPIDS  
DOC. NO. CPI: C1998-044167  
TITLE: Composition for treating conditions caused by insulin  
agonists - e.g. **hypoglycemia** and glycogen  
diseases.  
DERWENT CLASS: B04 D16  
PATENT ASSIGNEE(S): (MITU) MITSUBISHI CHEM CORP  
COUNTRY COUNT: 1  
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
JP 10007586	A	19980113	(199813)*		7

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 10007586	A	JP 1996-142839	19960605

PRIORITY APPLN. INFO: JP 1996-108263 19960426

L3 ANSWER 5 OF 9 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN  
TI Improving insulin therapy: Achievements and challenges.  
AB Microvascular complications of diabetes can be forestalled by effective  
glycemic control. However, the inherent limitations of standard  
subcutaneous insulins reduce their ability to control glycemia without  
risk of significant **hypoglycemia** and hyperinsulinemia.  
**Hypoglycemia** is unacceptable for most patients and may be  
dangerous. Hyperinsulinemia is undesirable because it causes weight gain  
and it has a putative association with atherosclerosis. This paper  
summarizes the major historical improvements in insulin therapy, and calls  
attention to the fact that none of the presently available commercial

preparations in any combination is capable of simulating the profile of normal insulin secretion - the latter being regarded as the most effective means of normalizing glycemia. For this reason, a variety of new approaches to simulating the pharmacokinetics or glucodynamics of insulin secretion are under investigation. Fast-acting insulin analogues suitable for subcutaneous injection have been developed and appear to mimic the physiological insulin response more closely than standard insulins. Less progress has been made with basal insulins. Intravenous insulin has pharmacodynamic advantages but practical disadvantages of administration. Nasal insulin would be an attractive treatment modality only if its bioavailability could be significantly increased and its safety assured. Other interventions which improve glucose metabolism without necessarily simulating normal insulin secretion are under investigation. These include biosynthetic human C-peptide, insulin-like growth factor-1 and glucagon-like peptide 1 (7-36 amide).

ACCESSION NUMBER: 94381559 EMBASE  
DOCUMENT NUMBER: 1994381559  
TITLE: Improving insulin therapy: Achievements and challenges.  
AUTHOR: Galloway J.A.; Chance R.E.  
CORPORATE SOURCE: Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285, United States  
SOURCE: Hormone and Metabolic Research, (1994) 26/12 (591-598).  
ISSN: 0018-5043 CODEN: HMMRA2  
COUNTRY: Germany  
DOCUMENT TYPE: Journal; Conference Article  
FILE SEGMENT: 003 Endocrinology  
006 Internal Medicine  
037 Drug Literature Index  
LANGUAGE: English  
SUMMARY LANGUAGE: English

L3 ANSWER 6 OF 9 USPATFULL on STN  
TI Methods of treating diabetes mellitus  
AB Methods of treating diabetes mellitus in a patient in need of such treatment include administering an effective amount of an insulin drug to the patient in order to treat diabetes mellitus in the patient. Methods according to the present invention may "activate" the liver, potentially restoring normal glucose homeostasis to individuals suffering from diabetes mellitus.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:71941 USPATFULL  
TITLE: Methods of treating diabetes mellitus  
INVENTOR(S): Ekwuribe, Nnochiri N., Cary, NC, UNITED STATES  
Price, Christopher H., Chapel Hill, NC, UNITED STATES  
Still, James Gordon, Raleigh, NC, UNITED STATES  
Filbey, Jennifer Ann, Raleigh, NC, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003050228	A1	20030313
APPLICATION INFO.:	US 2002-75097	A1	20020213 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-269198P	20010215 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	MYERS BIGEL SIBLEY & SAJOVEC, PO BOX 37428, RALEIGH, NC, 27627	
NUMBER OF CLAIMS:	230	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	20 Drawing Page(s)	
LINE COUNT:	3140	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 7 OF 9 USPATFULL on STN  
TI Treatment of acute and chronic liver disease  
AB The present invention relates to IGF-1 treatment of an individual, such as e.g. a human being, suffering from an acute or chronic liver disease including hepatic cirrhosis. Acute and chronic liver disease according to the invention are characterized by low circulating IGF-1 and IGFBP3 levels. According to one preferred embodiment of the present invention, IGF-1 is administered to a human being subcutaneously, preferably in the thigh or the abdominal skin, and preferably in two daily doses of about 50 microgram/kg twice a day. The present invention demonstrates that this dosing regime is able to restore normal IGF-1 levels in patients with liver cirrhosis, and the dose is well-tolerated by the patients.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:48572 USPATFULL  
TITLE: Treatment of acute and chronic liver disease  
INVENTOR(S): Grofte, Thorbjorn, Viby J., DENMARK  
Vilstrup, Hendrik, Risskov, DENMARK  
PATENT ASSIGNEE(S): Aarhus Amt., Højbjerg, DENMARK (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002028764	A1	20020307
APPLICATION INFO.:	US 2001-928832	A1	20010814 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	DK 2000-1317	20000904
	US 2000-237715P	20001005 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	BROWDY AND NEIMARK, P.L.L.C., 624 Ninth Street, N.W., Washington, DC, 20001	
NUMBER OF CLAIMS:	22	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	5 Drawing Page(s)	
LINE COUNT:	3074	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 8 OF 9 USPATFULL on STN  
TI Amylin activity assays  
AB Novel methods for use in identifying or assaying compounds which can simulate the ability of amylin to cause hyperlactemia and hyperglycemia in in vivo biological models, or for use in evaluating the potency of compounds known or suspected to simulate these actions of amylin, which involve introducing test samples into in vivo test systems and determining the presence or amount of a rise in lactate, or determining the presence or amount of a rise in lactate and a rise in glucose, following test sample administration.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2000:43755 USPATFULL  
TITLE: Amylin activity assays  
INVENTOR(S): Young, Andrew A., San Diego, CA, United States  
Cooper, Garth J. S., Solana Beach, CA, United States  
Rink, Timothy J., La Jolla, CA, United States  
PATENT ASSIGNEE(S): Amylin Pharmaceuticals, Inc., San Diego, CA, United States (U.S. corporation)

NUMBER	KIND	DATE
-----		

PATENT INFORMATION: US 6048514 20000411  
 APPLICATION INFO.: US 1995-422747 19950414 (8)  
 RELATED APPLN. INFO.: Continuation of Ser. No. US 1993-88629, filed on 6 Jul 1993, now abandoned which is a continuation of Ser. No. US 1991-666527, filed on 8 Mar 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-640478, filed on 10 Jan 1991, now patented, Pat. No. US 5234906  
 DOCUMENT TYPE: Utility  
 FILE SEGMENT: Granted  
 PRIMARY EXAMINER: Russel, Jeffrey E.  
 LEGAL REPRESENTATIVE: Lyon & Lyon LLP  
 NUMBER OF CLAIMS: 12  
 EXEMPLARY CLAIM: 1  
 NUMBER OF DRAWINGS: 24 Drawing Figure(s); 15 Drawing Page(s)  
 LINE COUNT: 1915  
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 9 OF 9 USPATFULL on STN

TI Insulin receptor

AB Insulin receptor is purified in accordance with this invention to a level sufficient to enable amino acid sequencing thereof. DNA encoding insulin receptor is provided, as well as methods for synthesizing insulin receptor or its mutant in heterologous host cells transformed with vectors containing such DNA. Knowledge of the amino acid sequence for insulin receptor enables the preparation of novel immunogenic conjugates and antibodies raised against such conjugates. Novel therapeutically useful forms of the insulin receptor and anti-receptor antibodies are described.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 88:48719 USPATFULL

TITLE: Insulin receptor

INVENTOR(S): Bell, John R., San Francisco, CA, United States  
 Ramachandran, Janakiraman, Palo Alto, CA, United States  
 Ullrich, Axel, San Francisco, CA, United States  
 PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4761371		19880802
APPLICATION INFO.:	US 1985-700776		19850212 (6)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Wiseman, Thomas G.		
ASSISTANT EXAMINER:	Seidman, Stephanie		
NUMBER OF CLAIMS:	13		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	15 Drawing Figure(s); 14 Drawing Page(s)		
LINE COUNT:	1144		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d his

(FILE 'HOME' ENTERED AT 11:42:53 ON 04 AUG 2003)

FILE 'MEDLINE, BIOSIS, DGENE, WPIDS, JICST-EPLUS, FSTA, EMBASE, USPATFULL' ENTERED AT 11:45:22 ON 04 AUG 2003

L1 3052 S INSULIN () AGONIST  
 L2 54 S L1 AND ANTAGONIST  
 L3 9 S L1 AND HYPOGLYCEMIA



=> s l1 and hyperglycemia  
L4 16 L1 AND HYPERGLYCEMIA

=> d l4 ti abs ibib tot

L4 ANSWER 1 OF 16 MEDLINE on STN  
TI LeuB24]insulin is an **insulin agonist** at the liver in vivo.  
AB A mutant insulin isolated from the plasma of a diabetic patient has been reported to antagonize insulin action in vitro and was thought to be [LeuB24]insulin. This study examines the ability of [LeuB24]insulin to antagonize insulin action at the liver in vivo in anesthetized dogs. Antagonism of insulin action was first simulated by decreasing the intraportal insulin infusion 50%. This resulted in a significant increase in both glucose production (Ra) ( $\Delta = + 0.30 \pm 0.08 \text{ mg X kg}^{-1} \text{ X min}^{-1}$ ) and the glucose level in arterial plasma ( $\Delta = +6.5 \pm 2.8 \text{ mg/dl}$ ), validating the responsiveness of the preparation to partial insulin antagonism. [LeuB24]insulin was infused intraportally, at molar ratios of 1:1, 1:2, 1:4, and 1:10 (50, 25, 12.5, and 5 ng/min, respectively) with insulin (54 ng/min). Infusion at all but the lowest dose resulted in a significant drop in glucose production ( $\Delta = -0.44 \pm 0.07$ ,  $-0.35 \pm 0.06$ , and  $-0.28 \pm 0.08 \text{ mg X kg}^{-1} \text{ X min}^{-1}$  for 4 analogue infusions of 50, 25, and 12.5 ng/min, respectively) and plasma glucose levels ( $\Delta = -7 \pm 3$  and  $-3 \pm 1 \text{ mg/dl}$  for analogue infusions of 50 and 25 ng/min, respectively). No change in Rd (glucose disposal) was observed for either insulin withdrawal or [LeuB24]insulin infusion. We conclude that, at the liver in vivo, [LeuB24]insulin does not antagonize insulin action but rather acts as an **insulin agonist**. Its hepatic effects would not contribute to a diabetic hyperglycemia.

ACCESSION NUMBER: 84049738 MEDLINE  
DOCUMENT NUMBER: 84049738 PubMed ID: 6356934  
TITLE: LeuB24]insulin is an **insulin agonist** at the liver in vivo.  
AUTHOR: Figlewicz D P; Best J D; Tager H S; Taborsky G J Jr  
CONTRACT NUMBER: AM-12829 (NIADDK)  
AM-16008 (NIADDK)  
AM-17047 (NIADDK)  
+  
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1983 Nov) 245 (5 Pt 1) E483-8.  
Journal code: 0370511. ISSN: 0002-9513.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 198312  
ENTRY DATE: Entered STN: 19900319  
Last Updated on STN: 19970203  
Entered Medline: 19831217

L4 ANSWER 2 OF 16 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN  
TI LEUCINE B-24 INSULIN IS AN **INSULIN AGONIST** AT THE LIVER IN-VIVO.  
AB A mutant insulin isolated from the plasma of a diabetic patient has been reported to antagonize insulin action in vitro and was thought to be [LeuB24]insulin. The ability of [LeuB24]insulin to antagonize insulin action at the liver in vivo was examined in anesthetized dogs. Antagonism of insulin action was first simulated by decreasing the intraportal insulin infusion 50%. This resulted in a significant increase in both glucose production (Ra) ( $\Delta = +0.30 \pm 0.08 \text{ mg .cntdot. kg}^{-1} \text{ .cntdot. min}^{-1}$ ) and the glucose level in arterial plasma ( $\Delta = +6.5 \pm 2.8 \text{ mg/dl}$ ), validating the responsiveness of the preparation to partial insulin antagonism. [LeuB24]insulin was infused intraportally, at

molar ratios of 1:1, 1:2, 1:4 and 1:10 (50, 25, 12.5 and 5 ng/min, respectively) with insulin (54 ng/min). Infusion at all but the lowest dose resulted in a significant drop in glucose production ( $\Delta$  = -0.44  $\pm$  0.07, -0.35  $\pm$  0.06 and -0.28  $\pm$  0.08 mg  $\cdot$  cntdot. kg<sup>-1</sup>  $\cdot$  cntdot. min<sup>-1</sup> for analog infusions of 50, 25 and 12.5 ng/min, respectively) and plasma glucose levels ( $\Delta$  = -7  $\pm$  3 and -3  $\pm$  1 mg/dl for analog infusions of 50 and 25 ng/min, respectively). No change in Rd (glucose disposal) was observed for either insulin withdrawal or [LeuB24]insulin infusion. At the liver in vivo, [LeuB24]insulin does not antagonize insulin action but rather acts as an **insulin agonist**. Its hepatic effects would not contribute to a diabetic

#### **hyperglycemia.**

ACCESSION NUMBER: 1984:233654 BIOSIS  
DOCUMENT NUMBER: BA77:66638  
TITLE: LEUCINE B-24 INSULIN IS AN **INSULIN AGONIST** AT THE LIVER IN-VIVO.  
AUTHOR(S): FIGLEWICZ D P; BEST J D; TAGER H S; TABORSKY G J JR  
CORPORATE SOURCE: DIV. ENDOCRINOL. METABOLISM, VETERANS ADM. MED. CENT., SEATTLE, WASH. 98108, USA.  
SOURCE: AM J PHYSIOL, (1983) 245 (5 PART 1), E483-E488.  
CODEN: AJPHAP. ISSN: 0002-9513.  
FILE SEGMENT: BA; OLD  
LANGUAGE: English

L4 ANSWER 3 OF 16 DGENE COPYRIGHT 2003 THOMSON DERWENT on STN  
TI New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
AN AAR82937 Protein DGENE  
AB Mouse Kv1.7 is a Shaker-related voltage-gated potassium channel (see Fig 1B). It may be used in drug screening for identification of therapeutics which modulate the channel and, therefore, modulate insulin secretion. Selective antagonists increase insulin release and thereby reduce **hyperglycemia** associated with non-insulin-dependent diabetes mellitus.

ACCESSION NUMBER: AAR82937 Protein DGENE  
TITLE: New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
INVENTOR: Chandy G; Chandy K G; Gutman G A; Kalman K  
PATENT ASSIGNEE: (REGC)UNIV CALIFORNIA.  
PATENT INFO: WO 9523858 A1 19950908 38p  
APPLICATION INFO: WO 1995-US2221 19950223  
PRIORITY INFO: US 1994-288405 19940810  
US 1994-207401 19940304  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
OTHER SOURCE: 1995-320573 [41]  
CROSS REFERENCES: N-PSDB: AAT04953  
DESCRIPTION: Mouse Kv1.7 voltage-gated potassium channel.

L4 -ANSWER 4 OF 16 DGENE COPYRIGHT 2003 THOMSON DERWENT on STN  
TI New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
AN AAT04957 DNA DGENE  
AB This primer is derived from the sequence of the mouse Kv1.7 voltage-gated potassium channel genomic clone (see AAT04953) and corresponds to the 3'-5' complementary sequence of the carboxy terminus of the S3-S4 loop. It is used with the upstream primer AAT04956 to amplify random primed cDNA generated from total RNA isolated from mouse brain and from the hamster insulinoma cell line, HIT-T15. The potassium channel may be used in drug screening for identification of therapeutics which modulate the channel and, therefore, modulate insulin secretion. Selective

antagonists increase insulin release and thereby reduce **hyperglycemia** associated with non-insulin-dependent diabetes mellitus.

ACCESSION NUMBER: AAT04957 DNA DGENE  
TITLE: New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
INVENTOR: Chandy G; Chandy K G; Gutman G A; Kalman K  
PATENT ASSIGNEE: (REGC)UNIV CALIFORNIA.  
PATENT INFO: WO 9523858 A1 19950908 38p  
APPLICATION INFO: WO 1995-US2221 19950223  
PRIORITY INFO: US 1994-288405 19940810  
US 1994-207401 19940304  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
OTHER SOURCE: 1995-320573 [41]  
DESCRIPTION: Downstream primer for mouse Kv1.7 potassium channel gene amplification.

L4 ANSWER 5 OF 16 DGENE COPYRIGHT 2003 THOMSON DERWENT on STN  
TI New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
AN AAT04956 DNA DGENE  
AB This primers is derived from the sequence of the mouse Kv1.7 voltage-gated potassium channel genomic clone (see AAT04953) and corresponds to the sequence in the S1 transmembrane segment. It is used with the downstream primer AAT04957 to amplify random primed cDNA generated from total RNA isolated from mouse brain and from the hamster insulinoma cell line, HIT-T15. The potassium channel may be used in drug screening for identification of therapeutics which modulate the channel and, therefore, modulate insulin secretion. Selective antagonists increase insulin release and thereby reduce **hyperglycemia** associated with non-insulin-dependent diabetes mellitus.

ACCESSION NUMBER: AAT04956 DNA DGENE  
TITLE: New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
INVENTOR: Chandy G; Chandy K G; Gutman G A; Kalman K  
PATENT ASSIGNEE: (REGC)UNIV CALIFORNIA.  
PATENT INFO: WO 9523858 A1 19950908 38p  
APPLICATION INFO: WO 1995-US2221 19950223  
PRIORITY INFO: US 1994-288405 19940810  
US 1994-207401 19940304  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
OTHER SOURCE: 1995-320573 [41]  
DESCRIPTION: Upstream primer for mouse Kv1.7 potassium channel gene amplification.

L4 ANSWER 6 OF 16 DGENE COPYRIGHT 2003 THOMSON DERWENT on STN  
TI New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
AN AAT04955 DNA DGENE  
AB Genomic sequences AAT04954-55 of mouse Kv1.7 voltage-gated potassium channel (see AAT04953) show the splice donor and acceptor sites which form the boundaries of the single intervening sequence (see Fig 1A). These sequences are compared with that of mouse (mKv1.7 and hamster (haKv1.7) cDNAs. The potassium channel may be used in drug screening for identification of therapeutics which modulate the channel and, therefore, modulate insulin secretion. Selective antagonists increase insulin release and thereby reduce **hyperglycemia** associated with non-insulin-dependent diabetes mellitus.

ACCESSION NUMBER: AAT04955 DNA DGENE  
 TITLE: New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
 INVENTOR: Chandy G; Chandy K G; Gutman G A; Kalman K  
 PATENT ASSIGNEE: (REGC)UNIV CALIFORNIA.  
 PATENT INFO: WO 9523858 A1 19950908 38p  
 APPLICATION INFO: WO 1995-US2221 19950223  
 PRIORITY INFO: US 1994-288405 19940810  
 US 1994-207401 19940304  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 OTHER SOURCE: 1995-320573 [41]  
 DESCRIPTION: Splice site for mouse Kv1.7 voltage-gated potassium channel.

L4 ANSWER 7 OF 16 DGENE COPYRIGHT 2003 THOMSON DERWENT on STN  
 TI New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
 AN AAT04954 DNA DGENE  
 AB Genomic sequences AAT04954-55 of mouse Kv1.7 voltage-gated potassium channel (see AAT04953) show the splice donor and acceptor sites which form the boundaries of the single intervening sequence (see Fig 1A). These sequences are compared with that of mouse (mKv1.7 and hamster (hKv1.7) cDNAs. The potassium channel may be used in drug screening for identification of therapeutics which modulate the channel and, therefore, modulate insulin secretion. Selective antagonists increase insulin release and thereby reduce **hyperglycemia** associated with non-insulin-dependent diabetes mellitus.

ACCESSION NUMBER: AAT04954 DNA DGENE  
 TITLE: New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
 INVENTOR: Chandy G; Chandy K G; Gutman G A; Kalman K  
 PATENT ASSIGNEE: (REGC)UNIV CALIFORNIA.  
 PATENT INFO: WO 9523858 A1 19950908 38p  
 APPLICATION INFO: WO 1995-US2221 19950223  
 PRIORITY INFO: US 1994-288405 19940810  
 US 1994-207401 19940304  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 OTHER SOURCE: 1995-320573 [41]  
 DESCRIPTION: Splice site for mouse Kv1.7 voltage-gated potassium channel.

L4 ANSWER 8 OF 16 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN  
 TI A composition comprises one insulin secretagogue such as a sulfonylurea antidiabetic agent and FBPase inhibitor useful for the treatment of diabetes.  
 AN 2002-241412 [29] WPIDS  
 AB WO 200203978 A UPAB: 20020508  
 NOVELTY - A composition comprises one insulin secretagogue such as a sulfonylurea antidiabetic agent (I) and FBPase inhibitor (IIa) or (IIb).  
 DETAILED DESCRIPTION - A composition comprises one insulin secretagogue such as a sulfonylurea antidiabetic agent of formula (I) and FBPase inhibitor of formula (IIa) or (IIb), where in vivo or in vitro compounds of (IIa) and (IIb) are converted to M-PO32-, which inhibits FBPase:  
 A = e.g. H, halo or cycloalkyl;  
 B = e.g. alkyl or cycloalkyl;  
 Y = O or NR6;  
 R1 = e.g. (with proviso that when Y is O, the R1 is attached to O) H, alkyl, optionally substituted aryl or alicyclic, where cyclic moiety comprises carbonate, thiocarbonate or optionally substituted arylalkyl;  
 Y = e.g. NR6 (R1 attached to NR6 is selected from H or

$(C(R_2)_2)_q-COOR_3$ ;  
 $q = 1$  or  $2$ ;  
 when only one Y is O (where O is not part of a cyclic group containing the other Y), the other Y is  $N(R_{18})-(CR_{12}R_{13})-C(O)-R_{14}$ ; and when Y is O or  $NR_6$ , together  $R_1$  and  $R_1$  are alkyl-S-S-alkyl and form a cyclic group, or  $R_1$  and  $R_1$  together form a group of formula (a), (b) or (c);  
 $V =$  e.g. aryl or heteroaryl (optionally substituted) or 1-alkynyl;  
 $V+Z =$  connected via additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, where the cyclic group is fused to an aryl at the beta or gamma position to the Y adjacent to V;  
 $Z =$  e.g.  $CHR_2OH$  or  $CHR_2OC(O)R_3$ ;  
 $p = 2$  or  $3$ ;  
 $Z+W =$  connected via additional 3-5 atoms forms a cyclic group, optionally containing 1 heteroatom, and V must be optionally substituted aryl or heteroaryl;  
 $T =$  e.g. H, alkyl or aralkyl;  
 $W, W' = T$ ;  
 $W+W' =$  connected via additional 2-5 atoms forms a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl or optionally substituted aryl or heteroaryl;  
 $V_2, W_2, W'' = T$ ;  
 $Z_2 =$  e.g.  $CHR_2OH$  or  $CHR_2OC(O)R_3$ ;  
 $V_2+Z_2 =$  connected via additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally containing 1 heteroatom substituted by OH, acyloxy, alkoxycarbonyloxy or aryloxycarbonyl attached to a C that is 3 times atoms from a Y attached to phosphorus;  
 $Z' =$  e.g. OH,  $OC(O)R_3$  or  $OCO_2R_3$ ;  
 $D' = H$ ;  
 $D'' = H, \text{ alkyl, } OR_2 \text{ or } OH$ ;  
 $W_3 = T$  with the proviso that V, Z, W,  $W'$  are not all H and  $V_2, Z_2, W_2, W''$  are not all H;  
 $R_2 = R_3$  or H;  
 $R_3 =$  alkyl or alicyclic;  
 $R_4 = H$  or alkylene;  
 $R_4+R_4 =$  are connected via 2-6 atoms, optionally including one heteroatom selected from O, N or S;  
 $R_6 = H$  or acyloxyalkyl;  
 $n = 1-3$ ;  
 $R_{18} =$  e.g. H or aralkyl;  
 $R_{12}+R_{18} =$  connected via 1-4C form a cyclic group;  
 $R_{12}, R_{13} =$  e.g. H or lower aralkyl (all optionally substituted);  
 $R_{12}+R_{13} =$  connected via 2-6 C, optionally includes 1 heteroatom selected from O, N or S to form a cyclic group;  
 $R_{14} = OR_{17}, N(R_{17})_2, NHR_{17}, SR_{17}$  or  $NR_2R_{20}$ ;  
 $R_{15} =$  e.g. H, lower alkyl or lower aralkyl;  
 $R_{15}+R_{16} =$  are connected via 2-6 atoms to form a cyclic group, where the cyclic optionally includes one heteroatom selected from O, N or S;  
 $R_{16} =$  e.g.  $(CR_{12}R_{13})_n-C(O)-R_{14}$  or H;  
 $R_{17} =$  lower alkyl, lower aryl, lower aralkyl, or when  $R_{14}$  is  $N(R_{17})_2$ , together, both  $R_{17}$ s are connected via 2-6 atoms to form a cyclic, where the cyclic group optionally includes one heteroatom selected from O, N or S;  
 $R_{20} = H, \text{ lower } R_3 \text{ or } C(O)\text{-lower } R_3$ ;  
 $M =$  groups of formula (i), (ii), (iii), (iv) or  $-X-R_5$ , their salts or prodrugs:  
 $A, E, L =$  e.g.  $NR_{82}, NO_2, H, OR_7$  or  $SR_7$ ;  
 $A+L =$  cyclic group;  
 $L+E =$  cyclic group;  
 $E+J =$  e.g. cyclic group selected from aryl or cyclic alkyl;  
 $J =$  e.g.  $NR_{82}, NO_2, H, OR_7, SR_7$  or  $C(O)NR_{42}$ ;  
 $J+Y =$  e.g. cyclic group selected from aryl or cyclic alkyl;  
 $X_3 =$  e.g. alkyl(OH), alkyl or alkynyl (all optionally substituted), with the proviso that  $X_3$  is not substituted with  $COOR_2, SO_2H$  or  $PO_3R_{22}$ ;

Y3 = e.g. H, alkyl or alkynyl, all except H are optionally substituted;  
 R4 = H, alkyl or together both R4's form a cyclic alkyl group;  
 R25 = lower alkyl, lower aryl, lower aralkyl, lower alicyclic;  
 R7 = e.g. H or C(O)R10;  
 R8 = e.g. H or C(O)R10 or together both R8s form a bidentate alkyl;  
 R10 = e.g. H, lower alkyl or NH2;  
 R11 = alkyl, aryl, NR22 or OR2;  
 U6, V6 = e.g. H or acyloxy;  
 U6+V6 = lower cyclic ring containing at least one O;  
 W6 = amino or lower alkyl amino;  
 Z6 = alkyl or halogen;  
 A2 = e.g. NR82, NHSO2R3 or OR25;  
 E2 = e.g. H, halo or NR72;  
 B5 = NH, N= or CH=;  
 D5 = groups of formula (A) or (B):  
 Q5 = -C= or -N-, with the proviso that, when B5 is NH, Q5 is -C= and D5 is (A); when B5 is CH=, Q5 is -N- and D5 is (A); and when B5 is -N=, D5 is (B) and Q5 is -C=;  
 R5 =

(Full definitions for R5 are given in Definitions field).

INDEPENDENT CLAIMS are also included for:

- (1) a method for treating a mammal with diabetes comprising administration of at least one insulin secretagogue and FBPase inhibitor;
- (2) a composition comprising alpha-glucosidase inhibitor and FBPase inhibitor;
- (3) a composition comprising FBPase inhibitor, hepatic glucose output inhibitor selected from glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists, amylin agonists or fatty acid oxidation inhibitors; and
- (4) a method for treating mammal with diabetes comprising administration of an insulin, insulin analogue, biguanide, hepatic glucose output inhibitor or alpha-glucosidase inhibitor and FBPase inhibitor.

ACTIVITY - Antidiabetic; anorectic.

MECHANISM OF ACTION - Glycogen phosphorylase inhibitors; glucose-6-phosphatase inhibitor; glucagon antagonist; amylin agonist; fatty acid oxidation inhibitor; FBPase inhibitor GLP-1 receptor agonist; DPP-IV inhibitor.

Glucose-6-phosphatase inhibitors have and IC50 of 0.1 nM to 10 micro M (more preferably 0.1 nM to 200 nM).

USE - The invention is used to treat hyperglycemia, obesity, where the mammal has brittle diabetic, NIDDM (non-insulin dependent diabetes mellitus) or IDDM (insulin dependent diabetes mellitus) (all claimed).

ADVANTAGE - The combination effect of administering one FBPase inhibitor and one antidiabetic agent results in improvements in insulin sensitivity and/or insulin secretion beyond those observed for either agent alone, as well as provide beneficial effects on carbohydrate and/or lipid (e.g. fat) and/or protein metabolism, or may result in greater glycemic control.

In certain therapies the combination effects achieve similar benefits as observed by therapies alone but use significantly lower doses of that therapy, which is beneficial when potentially adverse effects are associated with that therapy.

Insulin secretagogues, FBPase inhibitors are efficacious both in early stages and advanced stages of diabetes.

The combination therapy has the ability to improve the primary response rate and in addition has the ability to reduce, delay or prevent the incidence of secondary failure.

Dwg.0/0

ACCESSION NUMBER: 2002-241412 [29] WPIDS  
 DOC. NO. CPI: C2002-072572  
 TITLE: A composition comprises one insulin secretagogue such as a sulfonylurea antidiabetic agent and FBPase inhibitor useful for the treatment of diabetes.

DERWENT CLASS: B05  
 INVENTOR(S): ERION, M D; FUJIWARA, T; VAN POELJE, P D  
 PATENT ASSIGNEE(S): (META-N) METABASIS THERAPEUTICS INC; (SANY) SANKYO CO LTD  
 COUNTRY COUNT: 96  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002003978	A2	20020117	(200229)	* EN	392
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001073271	A	20020121	(200234)		
NO 2003000034	A	20030305	(200329)		
CZ 2003000005	A3	20030514	(200337)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002003978	A2	WO 2001-US21557	20010705
AU 2001073271	A	AU 2001-73271	20010705
NO 2003000034	A	WO 2001-US21557	20010705
		NO 2003-34	20030103
CZ 2003000005	A3	WO 2001-US21557	20010705
		CZ 2003-5	20010705

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001073271	A Based on	WO 200203978
CZ 2003000005	A3 Based on	WO 200203978

PRIORITY APPLN. INFO: US 2000-216531P 20000706

L4 ANSWER 9 OF 16 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. on STN  
 TI [Leu(B24)]insulin is an **insulin agonist** at the liver  
 in vivo.  
 AB A mutant insulin isolated from the plasma of a diabetic patient has been  
 reported to antagonize insulin action in vitro and was thought to be  
 [Leu(B24)]insulin. This study examines the ability of [Leu(B24)]insulin to  
 antagonize insulin action at the liver in vivo in anesthetized dogs.  
 Antagonism of insulin action was first simulated by decreasing the  
 intraportal insulin infusion 50%. This resulted in a significant increase  
 in both glucose production (R(a)) (.DELTA. = +0.30 .+- . 0.08  
 mg.kg-1.min-1) and the glucose level in arterial plasma (.DELTA. = +6.5  
 .+- . 2.8 mg/dl), validating the responsiveness of the preparation to  
 partial insulin antagonism. [Leu(B24)]insulin was infused intraportally,  
 at molar ratios of 1:1, 1:2, 1:4, and 1:10 (50, 25, 12.5, and 5 ng/min,  
 respectively) with insulin (54 ng/min). Infusion at all but the lowest  
 dose resulted in a significant drop in glucose production (.DELTA. = -0.44  
 .+- . 0.07, -0.35 .+- . 0.06, and -0.28 .+- . 0.08 mg.kg.min-1 for analogue  
 infusions of 50, 25, and 12.5 ng/min, respectively), and plasma glucose  
 levels (.DELTA. = -7 .noteq. 3 and -3 .+- . 1 mg/dl for analogue infusions  
 of 50 and 25 ng/min, respectively. No change in R(d) (glucose disposal)  
 was observed for either insulin withdrawal or [Leu(B24)]insulin infusion.  
 We conclude that, at the liver in vivo, [Leu(B24)]insulin does not  
 antagonize insulin action but rather acts as an **insulin**  
**agonist**. Its hepatic effects would not contribute to a diabetic  
**hyperglycemia**.

ACCESSION NUMBER: 84015260 EMBASE  
 DOCUMENT NUMBER: 1984015260  
 TITLE: [Leu(B24)]insulin is an insulin agonist  
 at the liver in vivo.  
 AUTHOR: Figlewicz D.P.; Best J.D.; Tager H.S.; Taborsky Jr. G.J.  
 CORPORATE SOURCE: Division of Endocrinology and Metabolism, Veterans  
 Administration Medical Center, Seattle, WA 98108, United  
 States  
 SOURCE: American Journal of Physiology - Endocrinology and  
 Metabolism, (1983) 8/5 (E483-E488).  
 CODEN: AJPMMD  
 COUNTRY: United States  
 DOCUMENT TYPE: Journal  
 FILE SEGMENT: 037 Drug Literature Index  
 002 Physiology  
 003 Endocrinology  
 023 Nuclear Medicine  
 LANGUAGE: English

L4 ANSWER 10 OF 16 USPATFULL on STN  
 TI Methods of treating diabetes mellitus  
 AB Methods of treating diabetes mellitus in a patient in need of such  
 treatment include administering an effective amount of an insulin drug  
 to the patient in order to treat diabetes mellitus in the patient.  
 Methods according to the present invention may "activate" the liver,  
 potentially restoring normal glucose homeostasis to individuals  
 suffering from diabetes mellitus.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:71941 USPATFULL  
 TITLE: Methods of treating diabetes mellitus  
 INVENTOR(S): Ekwuribe, Nnochiri N., Cary, NC, UNITED STATES  
 Price, Christopher H., Chapel Hill, NC, UNITED STATES  
 Still, James Gordon, Raleigh, NC, UNITED STATES  
 Filbey, Jennifer Ann, Raleigh, NC, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003050228	A1	20030313
APPLICATION INFO.:	US 2002-75097	A1	20020213 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-269198P	20010215 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	MYERS BIGEL SIBLEY & SAJOVEC, PO BOX 37428, RALEIGH, NC, 27627	
NUMBER OF CLAIMS:	230	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	20 Drawing Page(s)	
LINE COUNT:	3140	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 11 OF 16 USPATFULL on STN  
 TI IGF-I point variants  
 AB IGF-I and insulin variants are provided that selectively bind to IGFBP-1  
 or IGFBP-3. These agonist variants are useful, for example, to improve  
 the half-lives of IGF-I and insulin, respectively.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:20296 USPATFULL  
 TITLE: IGF-I point variants  
 INVENTOR(S): Dubaquié, Yves, San Francisco, CA, United States



PATENT ASSIGNEE(S): Lowman, Henry, El Granada, CA, United States  
Genentech, Inc., South San Francisco, CA, United States  
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6509443	B1	20030121
APPLICATION INFO.:	US 2000-723896		20001128 (9)
RELATED APPLN. INFO.:	Division of Ser. No. US 2000-477923, filed on 5 Jan 2000		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-115010P	19990106 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Kemmerer, Elizabeth	
ASSISTANT EXAMINER:	DeBerry, Regina M.	
LEGAL REPRESENTATIVE:	Hasak, Janet E.	
NUMBER OF CLAIMS:	3	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	13 Drawing Figure(s); 8 Drawing Page(s)	
LINE COUNT:	2509	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 12 OF 16 USPATFULL on STN  
TI IGF-I variants  
AB IGF-I and insulin variants are provided that selectively bind to IGFBP-1 or IGFBP-3. These agonist variants are useful, for example, to improve the half-lives of IGF-I and insulin, respectively.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
ACCESSION NUMBER: 2003:13376 USPATFULL  
TITLE: IGF-I variants  
INVENTOR(S): Dubaquié, Yves, San Francisco, CA, United States  
Lowman, Henry, El Granada, CA, United States  
PATENT ASSIGNEE(S): Genentech, Inc., South San Francisco, CA, United States  
(U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6506874	B1	20030114
APPLICATION INFO.:	US 2000-723981		20001128 (9)
RELATED APPLN. INFO.:	Division of Ser. No. US 2000-477923, filed on 5 Jan 2000, now patented, Pat. No. US 6403764		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-115010P	19990106 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Kunz, Gary L.	
ASSISTANT EXAMINER:	DeBerry, Regina M.	
LEGAL REPRESENTATIVE:	Hasak, Janet E.	
NUMBER OF CLAIMS:	13	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	13 Drawing Figure(s); 8 Drawing Page(s)	
LINE COUNT:	2540	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 13 OF 16 USPATFULL on STN  
TI Phosphoprotein target for insulin and its antagonists  
AB The invention provides methods for diagnosing and treating individuals with insulin resistance.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:343870 USPATFULL  
TITLE: Phosphoprotein target for insulin and its antagonists  
INVENTOR(S): Cooper, Garth J.S., Auckland, NEW ZEALAND  
Xu, Aimin, Auckland, NEW ZEALAND  
Wang, Yu, Auckland, NEW ZEALAND

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002197596	A1	20021226
APPLICATION INFO.:	US 2002-114540	A1	20020401 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-280584P	20010330 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	Randolph Ted Apple, Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA, 94304-1018	
NUMBER OF CLAIMS:	27	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	7 Drawing Page(s)	
LINE COUNT:	1346	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 14 OF 16 USPATFULL on STN

TI Treatment of acute and chronic liver disease

AB The present invention relates to IGF-1 treatment of an individual, such as e.g. a human being, suffering from an acute or chronic liver disease including hepatic cirrhosis. Acute and chronic liver disease according to the invention are characterized by low circulating IGF-1 and IGFBP3 levels. According to one preferred embodiment of the present invention, IGF-1 is administered to a human being subcutaneously, preferably in the thigh or the abdominal skin, and preferably in two daily doses of about 50 microgram/kg twice a day. The present invention demonstrates that this dosing regime is able to restore normal IGF-1 levels in patients with liver cirrhosis, and the dose is well-tolerated by the patients.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:48572 USPATFULL  
TITLE: Treatment of acute and chronic liver disease  
INVENTOR(S): Grofte, Thorbjorn, Viby J., DENMARK  
Vilstrup, Hendrik, Risskov, DENMARK  
PATENT ASSIGNEE(S): Aarhus Amt., Højbjerg, DENMARK (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002028764	A1	20020307
APPLICATION INFO.:	US 2001-928832	A1	20010814 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	DK 2000-1317	20000904
	US 2000-237715P	20001005 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	BROWDY AND NEIMARK, P.L.L.C., 624 Ninth Street, N.W., Washington, DC, 20001	
NUMBER OF CLAIMS:	22	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	5 Drawing Page(s)	
LINE COUNT:	3074	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 15 OF 16 USPATFULL on STN  
TI Amylin activity assays  
AB Novel methods for use in identifying or assaying compounds which can simulate the ability of amylin to cause hyperlactemia and **hyperglycemia** in in vivo biological models, or for use in evaluating the potency of compounds known or suspected to simulate these actions of amylin, which involve introducing test samples into in vivo test systems and determining the presence or amount of a rise in lactate, or determining the presence or amount of a rise in lactate and a rise in glucose, following test sample administration.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2000:43755 USPATFULL  
TITLE: Amylin activity assays  
INVENTOR(S): Young, Andrew A., San Diego, CA, United States  
Cooper, Garth J. S., Solana Beach, CA, United States  
Rink, Timothy J., La Jolla, CA, United States  
PATENT ASSIGNEE(S): Amylin Pharmaceuticals, Inc., San Diego, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6048514		20000411
APPLICATION INFO.:	US 1995-422747		19950414 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1993-88629, filed on 6 Jul 1993, now abandoned which is a continuation of Ser. No. US 1991-666527, filed on 8 Mar 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-640478, filed on 10 Jan 1991, now patented, Pat. No. US 5234906		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Russel, Jeffrey E.		
LEGAL REPRESENTATIVE:	Lyon & Lyon LLP		
NUMBER OF CLAIMS:	12		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	24 Drawing Figure(s); 15 Drawing Page(s)		
LINE COUNT:	1915		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 16 OF 16 USPATFULL on STN  
TI Transgenic mouse containing an IGF-1 transgene  
AB A transgenic mouse containing an IGF-1 transgene which is operably linked to a promoter sequence and is expressed in the pancreas of the mouse.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 1998:144270 USPATFULL  
TITLE: Transgenic mouse containing an IGF-1 transgene  
INVENTOR(S): Bosch, Fatima, Bellaterra, Spain  
Valera, Alfons, Bellaterra, Spain  
PATENT ASSIGNEE(S): The Autonomous University of Barcelona, Bellaterra, Spain (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5837875		19981117
APPLICATION INFO.:	US 1995-578245		19951226 (8)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-4260P	19950925 (60)

DOCUMENT TYPE: Utility  
FILE SEGMENT: Granted  
PRIMARY EXAMINER: Chambers, Jasmine C.  
ASSISTANT EXAMINER: Schmuck, Jill D.  
LEGAL REPRESENTATIVE: McGowan, WilliamFish & Richardson, Conway, John D.  
NUMBER OF CLAIMS: 7  
EXEMPLARY CLAIM: 1  
NUMBER OF DRAWINGS: 3 Drawing Figure(s); 2 Drawing Page(s)  
LINE COUNT: 695  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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(FILE 'HOME' ENTERED AT 11:42:53 ON 04 AUG 2003)

FILE 'MEDLINE, BIOSIS, DGENE, WPIDS, JICST-EPLUS, FSTA, EMBASE,  
USPATFULL' ENTERED AT 11:45:22 ON 04 AUG 2003

L1 3052 S INSULIN () AGONIST  
L2 54 S L1 AND ANTAGONIST  
L3 9 S L1 AND HYPOGLYCEMIA  
L4 16 S L1 AND HYPERGLYCEMIA

=> s l2 and l4

L5 8 L2 AND L4

=> d l5 ti abs ibib tot

L5 ANSWER 1 OF 8 DGENE COPYRIGHT 2003 THOMSON DERWENT on STN  
TI New voltage-gated potassium channel gene - used to identify material(s)  
which can increase insulin release e.g. for treating non-insulin  
dependent diabetes mellitus.  
AN AAR82937 Protein DGENE  
AB Mouse Kv1.7 is a Shaker-related voltage-gated potassium channel (see Fig  
1B). It may be used in drug screening for identification of therapeutics  
which modulate the channel and, therefore, modulate insulin secretion.  
Selective antagonists increase insulin release and thereby reduce  
**hyperglycemia** associated with non-insulin-dependent diabetes  
mellitus.

ACCESSION NUMBER: AAR82937 Protein DGENE  
TITLE: New voltage-gated potassium channel gene - used to identify  
material(s) which can increase insulin release e.g. for  
treating non-insulin dependent diabetes mellitus.  
INVENTOR: Chandy G; Chandy K G; Gutman G A; Kalman K  
PATENT ASSIGNEE: (REGC)UNIV CALIFORNIA.  
PATENT INFO: WO 9523858 A1 19950908 38p  
APPLICATION INFO: WO 1995-US2221 19950223  
PRIORITY INFO: US 1994-288405 19940810  
US 1994-207401 19940304  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
OTHER SOURCE: 1995-320573 [41]  
CROSS REFERENCES: N-PSDB: AAT04953  
DESCRIPTION: Mouse Kv1.7 voltage-gated potassium channel.

L5 ANSWER 2 OF 8 DGENE COPYRIGHT 2003 THOMSON DERWENT on STN  
TI New voltage-gated potassium channel gene - used to identify material(s)  
which can increase insulin release e.g. for treating non-insulin  
dependent diabetes mellitus.  
AN AAT04957 DNA DGENE  
AB This primer is derived from the sequence of the mouse Kv1.7 voltage-gated  
potassium channel genomic clone (see AAT04953) and corresponds to the  
3'-5' complementary sequence of the carboxy terminus of the S3-S4 loop.  
It is used with the upstream primer AAT04956 to amplify random primed

cDNA generated from total RNA isolated from mouse brain and from the hamster insulinoma cell line, HIT-T15. The potassium channel may be used in drug screening for identification of therapeutics which modulate the channel and, therefore, modulate insulin secretion. Selective antagonists increase insulin release and thereby reduce **hyperglycemia** associated with non-insulin-dependent diabetes mellitus.

ACCESSION NUMBER: AAT04957 DNA DGENE  
TITLE: New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
INVENTOR: Chandy G; Chandy K G; Gutman G A; Kalman K  
PATENT ASSIGNEE: (REGC)UNIV CALIFORNIA.  
PATENT INFO: WO 9523858 A1 19950908 38p  
APPLICATION INFO: WO 1995-US2221 19950223  
PRIORITY INFO: US 1994-288405 19940810  
US 1994-207401 19940304  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
OTHER SOURCE: 1995-320573 [41]  
DESCRIPTION: Downstream primer for mouse Kv1.7 potassium channel gene amplification.

L5 ANSWER 3 OF 8 DGENE COPYRIGHT 2003 THOMSON DERWENT on STN  
TI New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
AN AAT04956 DNA DGENE  
AB This primers is derived from the sequence of the mouse Kv1.7 voltage-gated potassium channel genomic clone (see AAT04953) and corresponds to the sequence in the S1 transmembrane segment. It is used with the downstream primer AAT04957 to amplify random primed cDNA generated from total RNA isolated from mouse brain and from the hamster insulinoma cell line, HIT-T15. The potassium channel may be used in drug screening for identification of therapeutics which modulate the channel and, therefore, modulate insulin secretion. Selective antagonists increase insulin release and thereby reduce **hyperglycemia** associated with non-insulin-dependent diabetes mellitus.

ACCESSION NUMBER: AAT04956 DNA DGENE  
TITLE: New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
INVENTOR: Chandy G; Chandy K G; Gutman G A; Kalman K  
PATENT ASSIGNEE: (REGC)UNIV CALIFORNIA.  
PATENT INFO: WO 9523858 A1 19950908 38p  
APPLICATION INFO: WO 1995-US2221 19950223  
PRIORITY INFO: US 1994-288405 19940810  
US 1994-207401 19940304  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
OTHER SOURCE: 1995-320573 [41]  
DESCRIPTION: Upstream primer for mouse Kv1.7 potassium channel gene amplification.

L5 ANSWER 4 OF 8 DGENE COPYRIGHT 2003 THOMSON DERWENT on STN  
TI New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
AN AAT04955 DNA DGENE  
AB Genomic sequences AAT04954-55 of mouse Kv1.7 voltage-gated potassium channel (see AAT04953) show the splice donor and acceptor sites which form the boundaries of the single intervening sequence (see Fig 1A). These sequences are compared with that of mouse (mKv1.7 and hamster (haKv1.7) cDNAs. The potassium channel may be used in drug screening for

identification of therapeutics which modulate the channel and, therefore, modulate insulin secretion. Selective antagonists increase insulin release and thereby reduce **hyperglycemia** associated with non-insulin-dependent diabetes mellitus.

ACCESSION NUMBER: AAT04955 DNA DGENE  
TITLE: New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
INVENTOR: Chandy G; Chandy K G; Gutman G A; Kalman K  
PATENT ASSIGNEE: (REGC)UNIV CALIFORNIA.  
PATENT INFO: WO 9523858 A1 19950908 38p  
APPLICATION INFO: WO 1995-US2221 19950223  
PRIORITY INFO: US 1994-288405 19940810  
US 1994-207401 19940304  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
OTHER SOURCE: 1995-320573 [41]  
DESCRIPTION: Splice site for mouse Kv1.7 voltage-gated potassium channel.

L5 ANSWER 5 OF 8 DGENE COPYRIGHT 2003 THOMSON DERWENT on STN  
TI New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
AN AAT04954 DNA DGENE  
AB Genomic sequences AAT04954-55 of mouse Kv1.7 voltage-gated potassium channel (see AAT04953) show the splice donor and acceptor sites which form the boundaries of the single intervening sequence (see Fig 1A). These sequences are compared with that of mouse (mKv1.7 and hamster (hKv1.7) cDNAs. The potassium channel may be used in drug screening for identification of therapeutics which modulate the channel and, therefore, modulate insulin secretion. Selective antagonists increase insulin release and thereby reduce **hyperglycemia** associated with non-insulin-dependent diabetes mellitus.

ACCESSION NUMBER: AAT04954 DNA DGENE  
TITLE: New voltage-gated potassium channel gene - used to identify material(s) which can increase insulin release e.g. for treating non-insulin dependent diabetes mellitus.  
INVENTOR: Chandy G; Chandy K G; Gutman G A; Kalman K  
PATENT ASSIGNEE: (REGC)UNIV CALIFORNIA.  
PATENT INFO: WO 9523858 A1 19950908 38p  
APPLICATION INFO: WO 1995-US2221 19950223  
PRIORITY INFO: US 1994-288405 19940810  
US 1994-207401 19940304  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
OTHER SOURCE: 1995-320573 [41]  
DESCRIPTION: Splice site for mouse Kv1.7 voltage-gated potassium channel.

L5 ANSWER 6 OF 8 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN  
TI A composition comprises one insulin secretagogue such as a sulfonylurea antidiabetic agent and FBPase inhibitor useful for the treatment of diabetes.  
AN 2002-241412 [29] WPIDS  
AB WO 200203978 A UPAB: 20020508  
NOVELTY - A composition comprises one insulin secretagogue such as a sulfonylurea antidiabetic agent (I) and FBPase inhibitor (IIa) or (IIb).  
DETAILED DESCRIPTION - A composition comprises one insulin secretagogue such as a sulfonylurea antidiabetic agent of formula (I) and FBPase inhibitor of formula (IIa) or (IIb), where in vivo or in vitro compounds of (IIa) and (IIb) are converted to M-PO32-, which inhibits FBPase:

A = e.g. H, halo or cycloalkyl;

B = e.g. alkyl or cycloalkyl;

Y = O or NR6;

R1 = e.g. (with proviso that when Y is O, the R1 is attached to O) H, alkyl, optionally substituted aryl or alicyclic, where cyclic moiety comprises carbonate, thiocarbonate or optionally substituted arylalkyl;  
 Y = e.g. NR6 (R1 attached to NR6 is selected from H or (C(R2)2)q-COOR3;  
 q = 1 or 2;  
 when only one Y is O (where O is not part of a cyclic group containing the other Y), the other Y is N(R18)-(CR12R13)-C(O)-R14; and when Y is O or NR6, together R1 and R1 are alkyl-S-S-alkyl and form a cyclic group, or R1 and R1 together form = a group of formula (a), (b) or (c);  
 V = e.g. aryl or heteroaryl (optionally substituted) or 1-alkynyl;  
 V+Z = connected via additional 3-5 atoms to form a cyclic group, optionally containing 1 heteroatom, where the cyclic group is fused to an aryl at the beta or gamma position to the Y adjacent to V;  
 Z = e.g. CHR2OH or CHR2OC(O)R3;  
 p = 2 or 3;  
 Z+W = connected via additional 3-5 atoms forms a cyclic group, optionally containing 1 heteroatom, and V must be optionally substituted aryl or heteroaryl;  
 T = e.g. H, alkyl or aralkyl;  
 W, W' = T;  
 W+W' = connected via additional 2-5 atoms forms a cyclic group, optionally containing 0-2 heteroatoms, and V must be aryl or optionally substituted aryl or heteroaryl;  
 V2, W2, W'' = T;  
 Z2 = e.g. CHR2OH or CHR2OC(O)R3;  
 V2+Z2 = connected via additional 3-5 atoms to form a cyclic group containing 5-7 atoms, optionally containing 1 heteroatom substituted by OH, acyloxy, alkoxycarbonyloxy or aryloxycarbonyl attached to a C that is 3 times atoms from a Y attached to phosphorus;  
 Z' = e.g. OH, OC(O)R3 or OCO2R3;  
 D' = H;  
 D'' = H, alkyl, OR2 or OH;  
 W3 = T with the proviso that V, Z, W, W' are not all H and V2, Z2, W2, W'' are not all H;  
 R2 = R3 or H;  
 R3 = alkyl or alicyclic;  
 R4 = H or alkylene;  
 R4+R4 = are connected via 2-6 atoms, optionally including one heteroatom selected from O, N or S;  
 R6 = H or acyloxyalkyl;  
 n = 1-3;  
 R18 = e.g. H or aralkyl;  
 R12+R18 = connected via 1-4C form a cyclic group;  
 R12, R13 = e.g. H or lower aralkyl (all optionally substituted);  
 R12+R13 = connected via 2-6 C, optionally includes 1 heteroatom selected from O, N or S to form a cyclic group;  
 R14 = OR17, N(R17)2, NHR17, SR17 or NR2R20;  
 R15 = e.g. H, lower alkyl or lower aralkyl;  
 R15+R16 = are connected via 2-6 atoms to form a cyclic group, where the cyclic optionally includes one heteroatom selected from O, N or S;  
 R16 = e.g. (CR12R13)n-C(O)-R14 or H;  
 R17 = lower alkyl, lower aryl, lower aralkyl, or when R14 is N(R17)2, together, both R17s are connected via 2-6 atoms to form a cyclic, where the cyclic group optionally includes one heteroatom selected from O, N or S;  
 R20 = H, lower R3 or C(O)-lower R3;  
 M = groups of formula (i), (ii), (iii), (iv) or -X-R5, their salts or prodrugs:  
 A, E, L = e.g. NR82, NO2, H, OR7 or SR7;  
 A+L = cyclic group;  
 L+E = cyclic group;  
 E+J = e.g. cyclic group selected from aryl or cyclic alkyl;

J = e.g. NR82, NO2, H, OR7, SR7 or C(O)NR42;  
 J+Y = e.g. cyclic group selected from aryl or cyclic alkyl;  
 X3 = e.g. alkyl(OH), alkyl or alkynyl (all optionally substituted),  
 with the proviso that X3 is not substituted with COOR2, SO2H or PO3R22;  
 Y3 = e.g. H, alkyl or alkynyl, all except H are optionally  
 substituted;  
 R4 = H, alkyl or together both R4's form a cyclic alkyl group;  
 R25 = lower alkyl, lower aryl, lower aralkyl, lower alicyclic;  
 R7 = e.g. H or C(O)R10;  
 R8 = e.g. H or C(O)R10 or together both R8s form a bidentate alkyl;  
 R10 = e.g. H, lower alkyl or NH2;  
 R11 = alkyl, aryl, NR22 or OR2;  
 U6, V6 = e.g. H or acyloxy;  
 U6+V6 = lower cyclic ring containing at least one O;  
 W6 = amino or lower alkyl amino;  
 Z6 = alkyl or halogen;  
 A2 = e.g. NR82, NHSO2R3 or OR25;  
 E2 = e.g. H, halo or NR72;  
 B5 = NH, N= or CH=;  
 D5 = groups of formula (A) or (B):  
 Q5 = -C= or -N-, with the proviso that, when B5 is NH, Q5 is -C= and  
 D5 is (A); when B5 is CH=, Q5 is -N- and D5 is (A); and when B5 is -N=, D5  
 is (B) and Q5 is -C=;  
 R5 =

(Full definitions for R5 are given in Definitions field).

INDEPENDENT CLAIMS are also included for:

- (1) a method for treating a mammal with diabetes comprising administration of at least one insulin secretagogue and FBPase inhibitor;
- (2) a composition comprising alpha-glucosidase inhibitor and FBPase inhibitor;
- (3) a composition comprising FBPase inhibitor, hepatic glucose output inhibitor selected from glycogen phosphorylase inhibitors, glucose-6-phosphatase inhibitors, glucagon antagonists, amylin agonists or fatty acid oxidation inhibitors; and
- (4) a method for treating mammal with diabetes comprising administration of an insulin, insulin analogue, biguanide, hepatic glucose output inhibitor or alpha-glucosidase inhibitor and FBPase inhibitor.

ACTIVITY - Antidiabetic; anorectic.

MECHANISM OF ACTION - Glycogen phosphorylase inhibitors; glucose-6-phosphatase inhibitor; glucagon antagonist; amylin agonist; fatty acid oxidation inhibitor; FBPase inhibitor GLP-1 receptor agonist; DPP-IV inhibitor.

Glucose-6-phosphatase inhibitors have and IC50 of 0.1 nM to 10 micro M (more preferably 0.1 nM to 200 nM).

USE - The invention is used to treat hyperglycemia, obesity, where the mammal has brittle diabetic, NIDDM (non-insulin dependent diabetes mellitus) or IDDM (insulin dependent diabetes mellitus) (all claimed).

ADVANTAGE - The combination effect of administering one FBPase inhibitor and one antidiabetic agent results in improvements in insulin sensitivity and/or insulin secretion beyond those observed for either agent alone, as well as provide beneficial effects on carbohydrate and/or lipid (e.g. fat) and/or protein metabolism, or may result in greater glycemic control.

In certain therapies the combination effects achieve similar benefits as observed by therapies alone but use significantly lower doses of that therapy, which is beneficial when potentially adverse effects are associated with that therapy.

Insulin secretagogues, FBPase inhibitors are efficacious both in early stages and advanced stages of diabetes.

The combination therapy has the ability to improve the primary response rate and in addition has the ability to reduce, delay or prevent the incidence of secondary failure.

Dwg. 0/0



DOC. NO. CPI: C2002-072572  
 TITLE: A composition comprises one insulin secretagogue such as a sulfonylurea antidiabetic agent and FBPase inhibitor useful for the treatment of diabetes.  
 DERWENT CLASS: B05  
 INVENTOR(S): ERION, M D; FUJIWARA, T; VAN POELJE, P D  
 PATENT ASSIGNEE(S): (META-N) METABASIS THERAPEUTICS INC; (SANY) SANKYO CO LTD  
 COUNTRY COUNT: 96  
 PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002003978	A2	20020117	(200229)*	EN	392
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2001073271	A	20020121	(200234)		
NO 2003000034	A	20030305	(200329)		
CZ 2003000005	A3	20030514	(200337)		

# APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002003978	A2	WO 2001-US21557	20010705
AU 2001073271	A	AU 2001-73271	20010705
NO 2003000034	A	WO 2001-US21557	20010705
		NO 2003-34	20030103
CZ 2003000005	A3	WO 2001-US21557	20010705
		CZ 2003-5	20010705

# FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001073271	A Based on	WO 200203978
CZ 2003000005	A3 Based on	WO 200203978

PRIORITY APPLN. INFO: US 2000-216531P 20000706

L5 ANSWER 7 OF 8 USPATFULL on STN  
 TI Phosphoprotein target for insulin and its antagonists  
 AB The invention provides methods for diagnosing and treating individuals with insulin resistance.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:343870 USPATFULL  
 TITLE: Phosphoprotein target for insulin and its antagonists  
 INVENTOR(S): Cooper, Garth J.S., Auckland, NEW ZEALAND  
 Xu, Aimin, Auckland, NEW ZEALAND  
 Wang, Yu, Auckland, NEW ZEALAND

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002197596	A1	20021226
APPLICATION INFO.:	US 2002-114540	A1	20020401 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-280584P	20010330 (60)
DOCUMENT TYPE:	Utility	

FILE SEGMENT: APPLICATION  
LEGAL REPRESENTATIVE: Randolph Ted Apple, Morrison & Foerster LLP, 755 Page  
Mill Road, Palo Alto, CA, 94304-1018  
NUMBER OF CLAIMS: 27  
EXEMPLARY CLAIM: 1  
NUMBER OF DRAWINGS: 7 Drawing Page(s)  
LINE COUNT: 1346  
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 8 OF 8 USPATFULL on STN  
TI Amylin activity assays  
AB Novel methods for use in identifying or assaying compounds which can simulate the ability of amylin to cause hyperlactemia and **hyperglycemia** in in vivo biological models, or for use in evaluating the potency of compounds known or suspected to simulate these actions of amylin, which involve introducing test samples into in vivo test systems and determining the presence or amount of a rise in lactate, or determining the presence or amount of a rise in lactate and a rise in glucose, following test sample administration.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.  
ACCESSION NUMBER: 2000:43755 USPATFULL  
TITLE: Amylin activity assays  
INVENTOR(S): Young, Andrew A., San Diego, CA, United States  
Cooper, Garth J. S., Solana Beach, CA, United States  
Rink, Timothy J., La Jolla, CA, United States  
PATENT ASSIGNEE(S): Amylin Pharmaceuticals, Inc., San Diego, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6048514		20000411
APPLICATION INFO.:	US 1995-422747		19950414 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1993-88629, filed on 6 Jul 1993, now abandoned which is a continuation of Ser. No. US 1991-666527, filed on 8 Mar 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-640478, filed on 10 Jan 1991, now patented, Pat. No. US 5234906		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Russel, Jeffrey E.		
LEGAL REPRESENTATIVE:	Lyon & Lyon LLP		
NUMBER OF CLAIMS:	12		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	24 Drawing Figure(s); 15 Drawing Page(s)		
LINE COUNT:	1915		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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(FILE 'HOME' ENTERED AT 11:42:53 ON 04 AUG 2003)

FILE 'MEDLINE, BIOSIS, DGENE, WPIDS, JICST-EPLUS, FSTA, EMBASE, USPATFULL' ENTERED AT 11:45:22 ON 04 AUG 2003

L1 3052 S INSULIN () AGONIST  
L2 54 S L1 AND ANTAGONIST  
L3 9 S L1 AND HYPOGLYCEMIA  
L4 16 S L1 AND HYPERGLYCEMIA  
L5 8 S L2 AND L4

=> s 12 and 13

L6 1 L2 AND L3

=> d 16 ti abs ibib tot

L6 ANSWER 1 OF 1 USPATFULL on STN  
TI Amylin activity assays  
AB Novel methods for use in identifying or assaying compounds which can simulate the ability of amylin to cause hyperlactemia and hyperglycemia in in vivo biological models, or for use in evaluating the potency of compounds known or suspected to simulate these actions of amylin, which involve introducing test samples into in vivo test systems and determining the presence or amount of a rise in lactate, or determining the presence or amount of a rise in lactate and a rise in glucose, following test sample administration.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2000:43755 USPATFULL  
TITLE: Amylin activity assays  
INVENTOR(S): Young, Andrew A., San Diego, CA, United States  
Cooper, Garth J. S., Solana Beach, CA, United States  
Rink, Timothy J., La Jolla, CA, United States  
PATENT ASSIGNEE(S): Amylin Pharmaceuticals, Inc., San Diego, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6048514		20000411
APPLICATION INFO.:	US 1995-422747		19950414 (8)
RELATED APPLN. INFO.:	Continuation of Ser. No. US 1993-88629, filed on 6 Jul 1993, now abandoned which is a continuation of Ser. No. US 1991-666527, filed on 8 Mar 1991, now abandoned which is a continuation-in-part of Ser. No. US 1991-640478, filed on 10 Jan 1991, now patented, Pat. No. US 5234906		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Russel, Jeffrey E.		
LEGAL REPRESENTATIVE:	Lyon & Lyon LLP		
NUMBER OF CLAIMS:	12		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	24 Drawing Figure(s); 15 Drawing Page(s)		
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.